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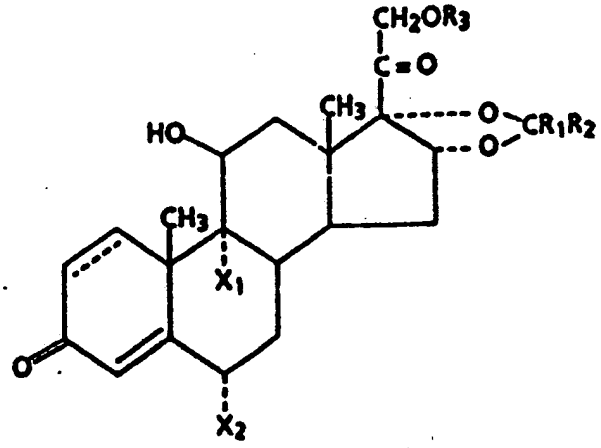
(54) Title: NOVEL STEROID ESTERS



(I)

(57) Abstract

Compounds of general formula (I), in which formula the 1,2-position is satured or is a double bond, R_1 is hydrogen or a straight or branched hydrocarbon chain, R_2 is a hydrogen or a straight or branched hydrocarbon chain, R_3 is acyl, X_1 is hydrogen or halogen, X_2 is hydrogen or halogen and provided that 1) R_1 and R_2 are not simultaneously hydrogen, 2) X_1 and X_2 are not simultaneously hydrogen, 3) when the 1,2-position is a double bonnd, R_1 and R_2 are not simultaneously methyl groups, 4) when the 1,2-position is a double bond, R_1 is a hydrogen atom and R_2 is a straight or branched hydrocarbon chain having 1-10 carbon atoms R_3 is acyl having 11-20 carbon atoms, processes for their preparation, pharmaceutical preparations containing them and the use of the compounds in the treatment of inflammatory and allergic conditions.

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Novel steroid esters

Field of invention

The present invention relates to novel anti-inflammatory and anti-allergic active compounds and to processes for their preparation. The invention also relates to pharmaceutical compositions containing the compounds and to methods of the pharmacological use of the composition.

The object of the invention is to provide an anti-inflammatory, immunosuppressive and anti-allergic glucocorticosteroid or a pharmaceutical composition thereof with high activity at the application place, e.g. in the respiratory tract, on the skin, in the intestinal tract, in the joints or in the eye, directing the drug to delimited target area, thereby inducing low glucocorticoid systemic effects.

A further object of the invention is to provide a pharmaceutical composition containing liposomes including a pharmacologically active steroid fatty acid ester of the invention in order to improve drug delivery and to minimize side effects of the therapy.

Background art

Glucocorticosteroids (GCS) are the most valuable drugs for relief of asthma and rhinitis. It is widely accepted that GCS exert their therapeutic efficacy by anti-inflammatory and anti-anaphylactic actions within airway and lung tissue. The long term oral use of GCS is greatly hampered by severe side effects outside the lung region. Accordingly, only a minor part of patients with asthma or rhinitis currently und rgo oral GCS therapy. A better

safety can be r ached by delivering GCS by inhalation. However, also th potent inhal d GCS in current wide clinical use - beclom thasone 17α,21-dipropionate and budesonide - have a rather narrow safety margin and for both unwanted GCS actions within the general circulation have been reported with the highest of the recommended doses for inhalation.

Liposomes are membrane-like vesicles consisting of series of concentric lipid bilayers alternating with hydrophilic compartments. Liposomes have been used as carriers for different kinds of pharmaceutically active compounds in order to improve drug delivery and to minimize side effects of the therapy.

Glucocorticosteroids are incorporated into liposomes only at a low concentration and are poorly retained in the vesicles. Esterification of GCS in 21-position with fatty acids increases the degree of incorporation and the retention of the steroid in the vesicles. It has been shown that the fatty acid chain acts as a hydrophobic "anchor" which holds the steroid nucleus in the hydrated polar head groups of the phospholipid and thereby improves the interaction between the glucocorticosteroid and the liposome.

Liposome-encapsulated glucocorticosteroids for therapeutic use have been described (M. De Silva et al., Lancet 8130 (1979), 1320) and US patent specification No 4 693 999 describes liposomal formulations of glucocorticosteroids for inhalation.

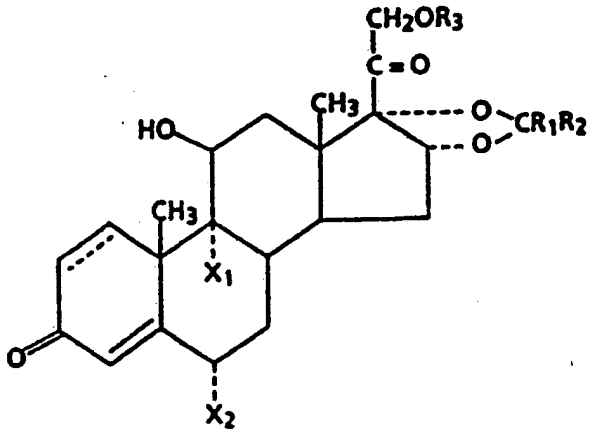
Disclosure of the invention

One object of the present invention is to provide new GCS compounds. The new compounds are charact rized by anti-inflammatory, immunosuppressiv and anti-anaphylactic

potency at the application sit and particularly they have a markedly improved relationship betw en that potency and the activity t provoke GCS actions outside the treated region. Th pr f rred mode of administration of the new compounds is by inhalation when the application site is within the airways.

Another object of the invention is to provide an anti-inflammatory and anti-allergic pharmaceutical composition containing steroid ester liposomes for local administration primarily to the respiratory tract. Such a composition provides for an improvement of the therapeutic properties of the steroid ester by a prolongation of the local retention in the airways and a direction of the drug to specific target cells.

The compounds of the invention are characterized by the formula



I

or a stereoisomeric component thereof, in which formula the 1,2-position is saturated or is a double bond,

R_1 is hydrogen or a straight or branched hydrocarbon chain having 1-4 carbon atoms,

R_2 is a hydrogen or a straight or branched hydrocarbon chain having 1-10 carbon atoms,

R_3 is a acyl having a straight or

branched, saturated or unsaturat d hydrocarbon chain having 1-20 carbon atoms,

X_1 is hydrogen or halogen

X_2 is hydrogen or halog n and

provided that

1) R_1 and R_2 are not simultaneously hydrogen,
2) X_1 and X_2 are not simultaneously hydrogen,
3) when the 1,2-position is a double bond, R_1 and R_2 are not simultaneously methyl groups,
4) when the 1,2-position is a double bond, R_1 is a hydrogen atom and R_2 is a straight or branched hydrocarbon chain having 1-10 carbon atoms R_3 is acyl having 11-20 carbon atoms.

The acyl is derived from

CH_3COOH:	acetic acid;
C_2H_5COOH:	propionic acid;
C_3H_7COOH:	butyric acid;
C_4H_9COOH:	valeric acid;
$C_5H_{11}COOH$:	hexanoic acid;
$C_6H_{13}COOH$:	heptanoic acid;
$C_7H_{15}COOH$:	octanoic acid;
$C_8H_{17}COOH$:	nonanoic acid;
$C_9H_{19}COOH$:	decanoic acid;
$C_{10}H_{19}COOH$:	capric acid;
$C_{11}H_{23}COOH$:	lauric acid;
$C_{12}H_{25}COOH$:	tridecanoic acid;
$C_{13}H_{27}COOH$:	myristic acid;
$C_{14}H_{29}COOH$:	pentadecanoic acid;
$C_{15}H_{31}COOH$:	palmitic acid;
$C_{16}H_{33}COOH$:	heptadecanoic acid;
$C_{17}H_{35}COOH$:	stearic acid;
$C_{17}H_{33}COOH$:	oleic acid;
$C_{17}H_{31}COOH$:	linolic acid;
$C_{17}H_{29}COOH$:	linolenic acid;

$C_{18}H_{37}COOH$: nonadecanoic acid;
$C_{19}H_{39}COOH$: icosanoic acid.

The preferred acylgroups are derived from

$C_{11}H_{23}COOH$: lauric acid;
$C_{13}H_{27}COOH$: myristic acid;
$C_{15}H_{31}COOH$: palmitic acid;
$C_{17}H_{35}COOH$: stearic acid;
$C_{17}H_{33}COOH$: oleic acid;
$C_{17}H_{31}COOH$: linolic acid;
$C_{17}H_{29}COOH$: linolenic acid,
and particularly it is palmitic acid.

A straight or branched hydrocarbon chain having 1-4 carbon atoms is preferably an alkyl group having 1-4 carbon atoms, particularly a methyl group.

A straight or branched hydrocarbon chain having 1-10 carbon atoms is preferably an alkyl group having 1-10 carbon atoms and preferably 1-4 carbon atoms, particularly a methyl or a propyl group.

A halogen atom in this specification is fluorine, chlorine or bromine. The preferred halogen atom is fluorine.

The preferred compounds of the invention are those where in formula I

the 1,2-position is saturated,
R_1 is hydrogen or a straight or branched hydrocarbon chain having 1-4 carbon atoms,
R_2 is a hydrogen or a straight or branched hydrocarbon chain having 1-10 carbon atoms,
R_3 is acyl having a straight or branched, saturated or unsaturated hydrocarbon chain having 1-20 carbon atoms,

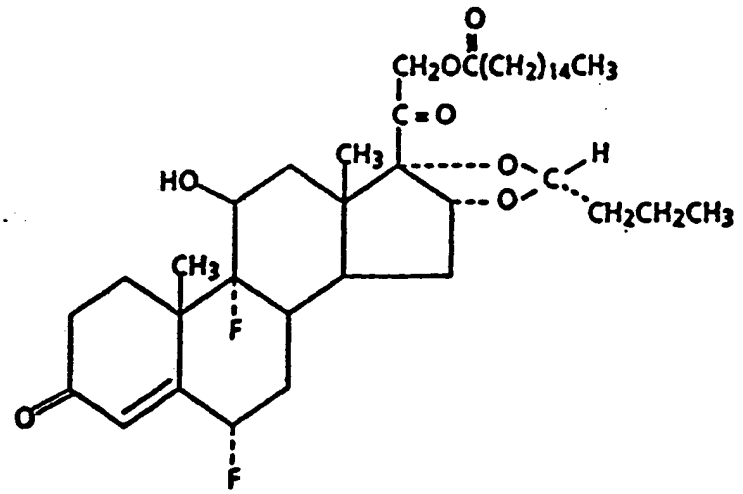
X_1 is hydrogen or halogen,
X_2 is hydrog n or halog n, and
provided that
1) R_1 and R_2 are not simultaneously hydrogen and
2) X_1 and X_2 are not simultaneously hydrogen.

Particularly preferred compounds of the invention are those where in formula I

the 1,2-position is saturated
R_1 is a hydrogen atom
R_2 is a propyl group
R_3 is acyl having 11-20 carbon atoms
X_1 is fluorine
X_2 is fluorine.

A further preferred compound of the invention is the one of the formula I wherein
the 1,2-position is a double bond,
R_1 is a hydrogen atom,
R_2 is a propyl group,
R_3 is a palmitoyl group,
X_1 is fluorine,
X_2 is fluorine.

The most preferred compound of the invention has the formula

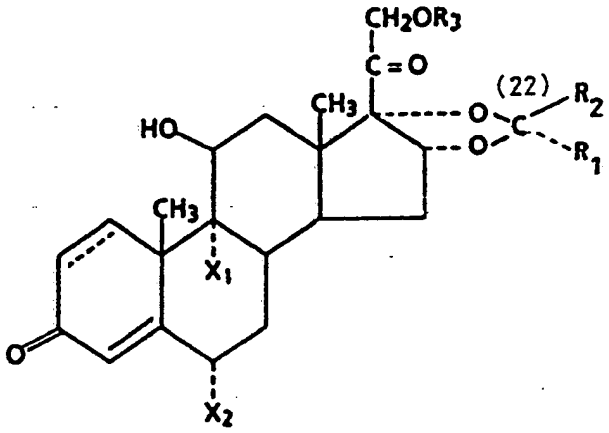


The preferred embodiment of the invention is a composition containing the preferred compound of the invention in combination with liposomes.

At instances where an object of the invention is to provide a pharmaceutical composition containing liposomes the active compound of the composition should be a compound of the formula I wherein R_3 is acyl having 11-20 carbon atoms.

At instances where an object of the invention is to provide a pharmaceutical composition without liposomes, the active compound of the composition should be a compound of the formula I wherein R_3 is acyl having 1-10 carbon atoms, preferably 5-10 carbon atoms.

The individual stereoisomeric components present in a mixture of a steroid having the above formula (I) can be elucidated in the following way due to the chirality at the carbon atom in 22-position and with respect to the R_2 substituent:



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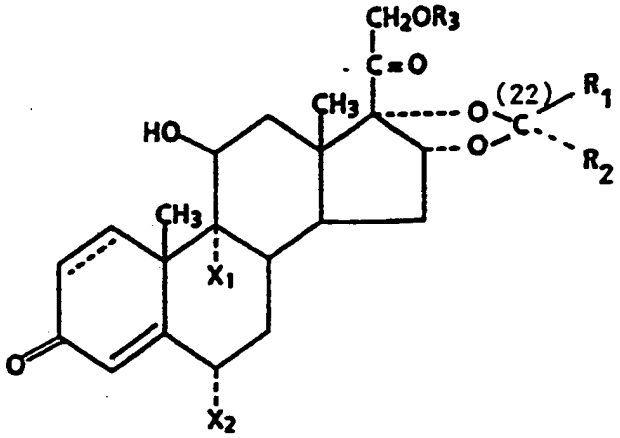
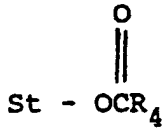


(epimer 22 R)

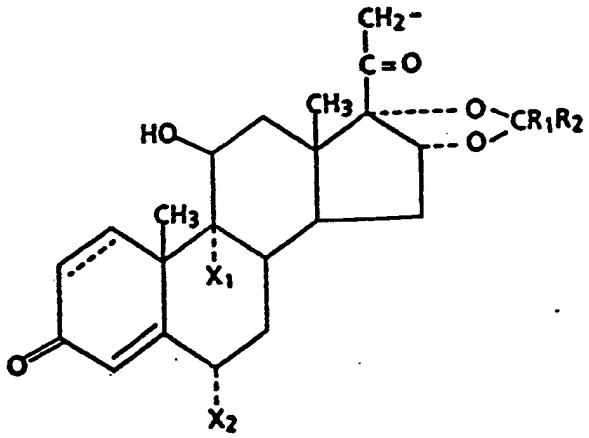
The preferred stereoisomeric component has the 22R configuration.

Methods of preparation

The steroid esters,



wherein St is



and X_1, X_2, R_1, R_2 have the meanings given above, R_4 is a straight or branched, saturated or unsaturated alkyl group with 1-19 carbon atoms and the 1,2-position is saturated or is a doubl bond, are prepared by any of the following alternative methods.

A. Reaction of a compound of the fomula

St-OH

wherein St has the definition given above, with a compound of the formula

wherein R_4 has the definition given above.

The esterification of the 21-hydroxy compound may be effected in known manner, e.g. by reacting the parent 21-hydroxy steroid with the appropriate carboxylic acid, advantageously in the presence of trifluoroacetic anhydride and preferably in the presence of an acid catalyst, e.g. p-toluenesulfonic acid.

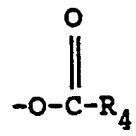
The reaction is advantageously performed in an organic solvent such as benzene or methylene chloride; the reaction being conveniently performed at a temperature of 20-100°C.

B. Reaction of a compound of the formula

St-OH

wherein St has th definition given above, with a compound of the formula

wherein R_4 has the definition given above, and X is a halogen atom, such as chlorine, bromine, iodine and fluorine, or the group



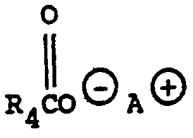
wherein R_4 has the definition given above.

The parent 21-hydroxy compound may be treated with the appropriate carboxylic acid halide or anhydride, preferably in a solvent such as halogenated hydrocarbons, e.g. methylene chloride or ethers, e.g. dioxane in the presence of a base such as triethylamine or pyridine, preferably at low temperature, e.g. -5°C to +30°C.

C. Reaction of a compound of the formula

St-Y

wherein St has the definition given above and Y is selected from halogen, e.g. Cl, Br and I, or from mesylate or p-toluenesulfonate, with a compound of the formula



wh r in R_4 has th definition giv n abov and $A^{\oplus}$ is a cation.

A salt of th appropriate carboxylic acid with an alkali metal, e.g. lithium, sodium or potassium, or a triethyl ammonium or tributylammonium salt may be reacted with the appropriate alkylating agent of the formula St-Y. The reaction is performed preferably in a polar solvent such as acetone, methylethyl ketone, dimethyl formamide or dimethyl sulfoxide, conveniently at a temperature in the range 25-100°C.

In any of methods A-C a final reaction step in order to resolve an epimeric mixture into its components may be necessary in case a pure epimer is desired.

Pharmaceutical preparations

The compounds of the invention may be used for different modes of local administration dependent on the site of inflammation, e.g. percutaneously, parenterally or for local administration in the respiratory tract by inhalation. An important aim of the formulation design is to reach optimal bioavailability of the active steroid ingredient. For percutaneous formulations this is advantagenously achieved if the steroid is dissolved with a high thermodynamic activity in the vehicle. This is attained by using a suitable system or solvents comprising suitable glycols, such as propylene glycol or 1,3-butandiol either as such or in combination with water.

It is also possible to dissolve the steroid either completely or partially in a lipophilic phase with the aid of a surfactant as a solubilizer. The percutaneous compositions can be an ointment, an oil in water cream, a water in oil cream or a lotion. In the emulsion vehicles the system comprising the dissolved active component can mak up the dispers phas as well as the continuous one.

The steroid can also exist in the above compositions as a micronized, solid substance.

Pressurized aerosols for steroids are intended for oral or nasal inhalation. The aerosol system is designed in such a way that each delivered dose contains 10-1000 µg, preferably 20-250 µg of the active steroid. The most active steroids are administered in the lower part of the dose range. The micronized steroid consists of particles substantially smaller than 5 µm, which are suspended in a propellent mixture with the assistance of a dispersant, such as sorbitan trioleate, oleic acid, lecithin or sodium salt of dioctylsulphosuccinic acid.

The steroid can also be administered by means of a dry powder inhaler.

One possibility is to mix the micronized steroid with a carrier substance such as lactose or glucose. The powder mixture is dispensed into hard gelatin capsules, each containing the desired dose of the steroid. The capsule is then placed in a powder inhaler and the dose is inhaled into the patient's airways.

Another possibility is to process the micronized powder into spheres which break up during the dosing procedure. This spheronized powder is filled into the drug reservoir in a multidose inhaler, e.g. Turbuhaler. A dosing unit meters the desired dose which is then inhaled by the patient. With this system the steroid with or without a carrier substance is delivered to the patient.

The steroid can also be included in formulations intended for treating inflammatory bowel diseases, either by the oral route or rectally. Formulations for the oral route should be constructed so that the steroid is delivered to the inflamed parts of the bowel. This can be accomplished

by different combinations of enteric and/or slow or control release principles. For the rectal route an enema type formulation is suitable.

Preparation of liposome compositions

The lecithins used in this invention have fatty acid chains of different lengths and therefore have different phase-transition temperatures. Examples of lecithins used are those derived from egg and soybean and synthetic lecithins like dimyristoyl phosphatidylcholine (DMPC), dipalmitoyl phosphatidylcholine (DPPC) and distearoyl phosphatidylcholine (DSPC). By manipulation of the structure lecithins stable carriers with variable biodegradable properties could be formulated. This would enable one to prolong the release of the entrapped steroid ester.

The extent of the interaction of the steroid ester with e.g. dipalmitoyl phosphatidylcholine (DPPC) vesicles is dependent on the ester chain length with increased interaction observed as the chain lengthens.

The inclusion of cholesterol or cholesterol derivatives in liposome formulations has become very common due to its properties in increasing liposome stability.

The initial stages of the preparation of liposomes according to the present invention may conveniently follow procedures described in the literature, i.e. the components being dissolved in a solvent, e.g. ethanol or chloroform which is then evaporated. The resulting lipid layer is then dispersed in the selected aqueous medium whereafter the solution is either shaken or sonicated. The liposomes of this invention preferably have a diameter of between 0.1 and 10 µm.

In addition to the main liposome-forming lipid(s) which is usually phospholipid, other lipids (e.g. cholesterol or chol sterol stearate) in the amount of 0-40% w/w of the total lipids may be includ d to modify the structure of the liposome membrane. In optimizing the uptake of the liposome a third component providing a negative charge (e.g. dipalmitoyl phosphatidyl glycerol) or a positive charge (e.g. stearylamine acetate or cetylpyridinium chloride) may be incorporated.

A wide range of proportions of steroid ester to lipid during formation may be used depending on the lipid and the conditions used. Drying, (freeze-drying or spray drying) of the liposomes in the presence of lactose can be used with a lactose content in the range of 0 to 95% of the final composition.

The composition according to the invention which is particularly preferred contains liposomes and (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione. The routes of administration involves powder aerosols, instillation, nebulization and pressurized aerosols.

Working examples

The invention will be further illustrated by the following non-limitative examples. In the examples a flow-rate of 2.5 $ml/cm^2 \cdot h^{-1}$ is used at the preparative chromatographic runs. Molecular weights are in all examples determined with chemical ionization mass spectrometry (CH_4 as reagent gas) and the melting points on a Leitz Wetzlar hot stage microscope. The HPLC analyses (High Performance Liquid Chromatography) have been performed on a μBondapak C_{18} column (300 x 3.9 mm i.d.) with a flow rate of 1.0 ml/min and with ethanol /water in ratios between 40:60 and 60:40 as mobile phase, if not otherwis stated.

Exampl 1. (22R)-16α,17α-Butylidenedi xy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregn-4- n -3,20-dion .

A solution of palmitoyl chloride (1.2 g) in 10 ml of dioxane was added drop-wise to a solution of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (200 mg) in 25 ml of pyridine. The reaction mixture was stirred for 16 h at room temperature. Methylene chloride (150 ml) was added and the solution washed with 1M hydrochloric acid, 5% aqueous potassium carbonate and water and dried. The crude product after evaporation was purified by chromatography on a Sephadex LH-20 column (87 x 2.5 cm) using chloroform as mobile phase. The fraction 210-255 ml was collected and evaporated leaving 203 mg of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyl-oxypregn-4-ene-3,20-dione. Melting point 87-90°C; molecular weight 706 (calc. 707.0). Purity: 96% (HPLC-analysis).

Example 2. (22R)-16α,17α-Butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione

To a solution of (22R)-16α,17α-butylidenedioxy-6α-9α-difluoro-11β, 21-dihydroxypregn-4-ene-3,20-dione (50 mg) and palmitoyl chloride (35 mg) in 10 ml of methylene chloride was added dropwise a solution of triethylamine (13 mg) in 2 ml of methylene chloride. The reaction mixture was stirred for 2 h at room temperature. Another 50 ml of methylene chloride was added and the reaction mixture was worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (85 x 2.5 cm) using chloroform as mobile phase. The fraction 210-250 ml was collected and evaporated yielding 34 mg of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione. Molecular weight 706

(calc. 707.0). Purity: 95% (HPLC-analysis).

Example 3. (22S)-16α,17α-Butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione.

A solution of palmitoyl chloride (0.4 ml) in 10 ml of dioxane was added drop-wise to a solution of (22S)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (70 mg) in 25 ml of pyridine. The reaction mixture was stirred for 16 h at room temperature and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (87 x 2.5 cm) using chloroform as mobile phase. The fraction 225-265 ml was collected and evaporated yielding 92 mg of (22S)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione as an oil. Molecular weight: 706 (calc. 707.0). Purity: 97% (HPLC-analysis).

Example 4. (22R)-16α,17α-Butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-myristoyloxypregn-4-ene-3,20-dione.

Myristoyl chloride was synthesized by refluxing myristic acid (7.0 g) and thionyl chloride (9 ml) in trichloroethylene (100 ml) for 3 h. The solvent was then evaporated.

To a solution of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (51 mg) in 10 ml of methylene chloride was added myristoyl chloride (32 mg) followed by triethylamine (13 mg) dissolved in methylene chloride (5 ml). The reaction mixture was stirred for 4 h at room temperature. Further methylene chloride was added and the mixture successively washed with 0.1M hydrochloric acid and water (3 x 50 ml). After drying and evaporation the residue was purified by chromatography on Merck Kieselgel 60 using h ptan :ac tone, 6:4, as mobile phas yi lding 27 mg of

(22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-myristoyloxypregn-4- n -3,20-dione. Mol cular weight 678 (calc. 678.9). Purity: 96.8% (HPLC-analysis).

Example 5. (22R)-16α,17α-Butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-lauroyloxypregn-4-ene-3,20-dione. To a solution of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (51 mg) in 5 ml of methylene chloride was added lauroyl chloride (28 mg) followed by triethylamine (13 mg) dissolved in 2 ml of methylene chloride. The reaction mixture was stirred at room temperature for 3 h, further methylene chloride was added and the organic phase washed successively with 0.1M hydrochloric acid and water (3 x 30 ml). After drying and evaporation the residue was purified by chromatography on Merck Kieselgel 60 using hexane:acetone, 6:4, as mobile phase. The product obtained was further purified in a second chromatographic step using petroleum ether:ethyl acetate, 3:2, as mobile phase yielding 33 mg of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-lauroyloxypregn-4-ene-3,20-dione. Molecular weight 650 (calc. 650.8). Purity: 96.9% (HPLC-analysis).

Example 6. (22R)-16α,17α-Butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregna-1,4-diene-3,20-dione.

A solution of palmitoyl chloride (2.3 ml) in 15 ml of dioxane was added drop-wise to a solution of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione (700 mg) in 30 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (76 x 6.3 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 1020-1350 ml was coll cted and

evaporated yielding 752 mg of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypr gna-1,4-di ne-3,20-dion . Melting point 141-145°C; $[\alpha]_D^{25}$ = +71.6° (c= 0.204; CH_2Cl_2); molecular weight 704 (calc. 704.9). Purity: 97.7% (HPLC-analysis).

Example 7. (22S)-16α,17α-Butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregna-1,4-diene-3,20-dione.

A solution of palmitoyl chloride (0.5 ml) in 5 ml of dioxane was added dropwise to a solution of (22S)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione (150 mg) in 10 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 215-315 ml was collected and evaporated yielding 132 mg of (22S)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregna-1,4-diene-3,20-dione. Melting point 176-180°C; $[\alpha]_D^{25}$ = +47.5° (c=0.198; CH_2Cl_2); molecular weight 704 (calc. 704.9). Purity: 99% (HPLC-analysis).

Example 8. (22R)-21-Acetoxy-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-pregn-4-ene-3,20-dione

A solution of acetyl chloride (38 mg) in 5 ml of dioxane was added dropwise to a solution of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (75 mg) in 5 ml of pyridine. The reaction mixture was stirred for 16h at room temperature. After evaporation methylene chloride (75 ml) was added and the solution was washed with cold 5% aqueous potassium carbonat and saturated sodium chloride solution. The crude product after vaporation was purified by

chromatography on a S phadex LH-20 column (85 x 2.5 cm) using chloroform as a mobile phase. The fraction 365-420 ml was collect d and vaporated 1 aving 57 mg of (22R)-21-acetoxy-16α,17α-butylid nedioxy-6α,9α-difluor -11β-hydroxypregn-4-ene-3,20-dione. Melting point 182-189°; $[\alpha]_D^{25}$ = +112.0° (c=0.225; CH_2Cl_2); molecular weight 510 (calc 510.6). Purity 99.0% (HPLC-analysis).

Example 9. (22R)-16α,17α-Butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-valeroyloxypregn-4-ene-3,20-dione

A solution of valeroyl chloride (60 mg) in 5 ml of dioxane was added dropwise to a solution of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (75 mg) in 5 ml of pyridine. The reaction mixture was stirred for 16h at room temperature. After evaporation methylene chloride (75 ml) was added and the solution was washed with cold 5% aqueous potassium carbonate and saturated sodium chloride solution. The crude product after evaporation was purified by chromatography on a Sephadex LH-20 column (85 x 2.5 cm) using chloroform as a mobile phase. The fraction 265-325 ml was collected and evaporated leaving 50 mg of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-valeroyloxypregn-4-ene-3,20-dione. Melting point 181-185°; $[\alpha]_D^{25}$ = +109.4° (c=0.212; CH_2Cl_2); molecular weight 552 (calc. 552.7). Purity 99.8% (HPLC-analysis).

Example 10. (22R)-16α,17α-Butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-capryloxypregna-1,4-diene-3,20-dione.

A solution of decanoyl chloride (0.2 ml) in 3 ml of dioxane was added dropwise to a solution of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione (100 mg) in 6 ml of pyridine. The

reaction mixture was stirred at room temperatur ov rnight and work d up as in Exampl 1. The crude product was purified on a Sephadex LH-20 column (71 x 6.3 cm) using chloroform as mobile phase. The fraction 1470-1725 ml was collected and evaporated yielding 113 mg of (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-capryloxypregna-1,4-diene-3,20-dione. Melting point 182-184°C. $[\alpha]_D^{25}$ = +71.5° (c=0.186; CH_2Cl_2). Molecular weight 620 (calc. 620.9). Purity: 97.7% (HPLC-analysis).

Example 11. 6α,9α-Difluoro-11β,21-dihydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione

A suspension of 0.9 g of tris(triphenylphosphine)rhodium chloride in 250 ml of degassed toluene was hydrogenated for 45 min at room temperature and atmospheric pressure. A solution of 1.0 g of fluocinolone 16α,17α-acetonide in 100 ml of absolute ethanol was added and the hydrogenation was continued for another 40 h. The reaction product was evaporated and the residue purified by flash chromatography on silica using acetone-petroleum ether as mobile phase to remove the main part of the catalyst. The eluate was evaporated and the residue further purified by chromatography on a Sephadex LH-20 column (72.5 x 6.3 cm) using chloroform as mobile phase. The fraction 3555-4125 ml was collected and evaporated yielding 0.61 g of 6α,9α-difluoro-11β,21-dihydroxy-16α,17α-[(1-methylethylidene)-bis(oxy)]pregn-4-ene-3,20-dione. Melting point 146-151°C. $[\alpha]_D^{25}$ = +124.5° (c=0.220;CH_2Cl_2). Molecular weight 454 (calc. 454.6). Purity: 98.5% (HPLC-analysis).

Example 12. 6α,9α-Difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-21-palmitoyloxypregn-4-ene-3,20-dione

A solution of palmitoyl chloride (2.1 ml) in 15 ml of dioxane was added dropwise to a solution of 6α,9α-difluor -11β,21-dihydroxy-16α,17α-[(1-methyl-

ethylidene)bis(oxy)]pr gn-4-ene-3,20-dion (310 mg) in 30 ml of pyridin . The reaction mixtur was stirred at room temperature ov rnight and work d up as in Example 1. The crude product was purified on a Sephadex LH-20 column (76 x 6.3 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 1035-1260 ml was collected and evaporated yielding 158 mg of 6α,9α-difluoro-11β-hydroxy-16α,17α[(1-methylethylidene)bis(oxy)]-21-palmitoyloxypregn-4-ene-3,20-dione. Melting point 82-86°C. $[\alpha]_D^{25}$ = +85.3° (c=0.232; CH_2Cl_2). Molecular weight 692 (calc. 692.9). Purity: 98.6% (HPLC-analysis).

Example 13. (22R)- and (22S)-21-Acetoxy-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxypregn-4-ene-3,20-dione

(22RS)-16α,17α-Butylidenedioxy-6α-fluoro-11β,21-dihydroxy-pregn-4-ene-3,20-dione (68 mg) was dissolved in 1 ml of pyridine. Acetic anhydride (1 ml) was added and the reaction mixture stirred at room temperature for 1 h, poured into ice-water and extracted with 3 x 25 ml of methylene chloride. The extract was dried and evaporated. The residual 22RS-mixture was resolved by chromatography on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fractions 380-400 ml (A) and 420-440 ml (B) were collected and evaporated.

After precipitation from methylene chloride - petroleum ether fraction A yielded 14 mg of (22S)-21-acetoxy-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxypregn-4-ene-3,20-dione. Melting point 179-186°C. $[\alpha]_D^{25}$ = +86.2° (c=0.188; CH_2Cl_2). Molecular weight 492 (calc. 492.6). Purity: 97.5% (HPLC-analysis).

Fraction B gave after precipitation 20 mg of (22R)-21-acetoxy-16α,17α-butylidenedi xy-6α-fluoro-11β-hydroxypregn-4-en -3,20-dione. Melting point 169-172°C.

$[\alpha]_D^{25}$ = +139.0° (c=0.200; CH_2Cl_2). Mol cular weight 492 (calc. 492.6). Purity: 97.9% (HPLC-analysis).

Example 14. (22RS)-16α,17α-Butylidenedioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione.

To a suspension of 1.4 g of tris(triphenylphosphine)-rhodium chloride in 300 ml of toluene was added a solution of 1170 mg of 6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione in 250 ml of absolute ethanol. The mixture was hydrogenated 22 h at room temperature and atmospheric pressure and evaporated. The residue was precipitated from acetone-chloroform yielding 661 mg of 6α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione. Molecular weight 396 (calc. 396.5). Purity: 96.6% (HPLC-analysis).

6α-Fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione (308 mg) was added in portions to a solution of butanal (115 mg) and 70% perchloric acid (0.2 ml) in 50 ml of dioxane. The reaction mixture was stirred at room temperature for 6 h. Methylene chloride (200 ml) was added and the solution washed with 10% aqueous potassium carbonate and water and dried. The residue after evaporation was purified on a Sephadex LH-20 column (87 x 2.5 cm) using chloroform as mobile phase. The fraction 420-500 ml was collected and evaporated yielding 248 mg of (22RS)-16α,17α-butylidenedioxy-6α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione. Melting point 85-96°C. $[\alpha]_D^{25}$ = +119.8° (c=0.192; CH_2Cl_2). Molecular weight 450 (calc. 450.6). Purity: 96.1% (HPLC-analysis). The distribution between the 22R- and 22S-epimers was 59/41 (HPLC-analysis).

A solution of palmitoyl chloride (0.21 ml) in 3 ml of dioxan was added dropwis to a solution of (22RS)-16α,17α-butylid nedioxy-6α-fluoro-11β,21-dihydroxypregn-4-

en -3,20-dion (50 mg) in 6 ml of pyridin . Th reaction mixtur was stirred at room temperature ov rnight and worked up as in Example 1. Th crude product was purified on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 185-230 ml was collected and evaporated yielding 42 mg of (22RS)-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione as an oil. Molecular weight 688 (calc. 688.97). Purity: 99.0% and the distribution between the 22R- and 22S-epimers was 15/85 (HPLC-analysis).

Example 15. (22R)-16α,17α-Butylidenedioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione. (22RS)-16α,17α-Butylidenedioxy-6α-fluoro-11β,21-diydroxypregn-4-ene-3,20-dione (225 mg) was resolved by preparative HPLC in portions on a μBondapak C_{18} column (150 x 19 mm) using ethanol:water, 40:60, as mobile phase. The fractions centered at 265 ml (A) and 310 ml (B) were collected and evaporated. After precipitation from methylene chloride - petroleum ether fraction A yielded 68 mg of (22R)-16α,17α-butylidenedioxy-6α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione. Melting point 180-192°C. $[\alpha]_D^{25}$ = +138.9° (c=0.144; CH_2Cl_2). Molecular weight 450 (calc. 450.6). Purity: 99.4% (HPLC-analysis).

Fraction B gave after precipitation 62 mg of (22S)-16α,17α-butylidenedioxy-6α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione. Melting point 168-175°C. $[\alpha]_D^{25}$ = +103.7° (c=0.216; CH_2Cl_2). Molecular weight 450 (calc. 450.6). Purity: 99.5% (HPLC-analysis).

A solution of palmitoyl chloride (0.22 ml) in 5 ml of dioxane was added dropwise to a solution of (22R)-16α,17α-butylidenedioxy-6α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (32 mg) in 10 ml of pyridine. The r action

mixtur was stirr d at room temp rature vernight and w rked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (87 x 2.5 cm) using chloroform as mobile phase. The fraction 215-250 ml was collected and evaporated yielding 38 mg of (22R)-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxy-pregn-4-ene-3,20-dione as an oil. Molecular weight 688 (calc. 688.97). Purity: 96.0% (HPLC-analysis)

Example 16. (22S)-16α,17α-Butylidenedioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione. (22RS)-16α,17α-Butylidenedioxy-6α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (68 mg) was dissolved in 1 ml of pyridine. Acetic anhydride (1 ml) was added and the reaction mixture stirred at room temperature for 1 h, poured into ice-water and extracted with 3 x 25 ml of methylene chloride. The extract was dried and evaporated. The residual 22RS epimeric mixtur was resolved by chromatography on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fractions 380-400 ml (A) and 420-440 ml (B) were collected and evaporated.

After precipitation from methylene chloride - petroleum ether fraction A yielded 14 mg of (22S)-21-acetoxy-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxypregn-4-ene-3,20-dione. Melting point 179-186°C. $[\alpha]_D^{25}$ = +86.2° (c=0.188; CH_2Cl_2). Molecular weight 492 (calc. 492.6). Purity: 97.5% (HPLC-analysis).

Fraction B gave after precipitation 20 mg of (22R)-21-acetoxy-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxypregn-4-ene-3,20-dione. Melting point 169-172°C. $[\alpha]_D^{25}$ = +139.0° (c=0.200; CH_2Cl_2 Molecular weight 492 (calc. 492.6). Purity: 97.9% (HPLC-analysis).

To a solution of 14 mg of (22S)-21-acetoxy-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxypregn-4-ene-3,20-dion in 2 ml of ethanol, 2 ml of 2M hydrochloric acid was added. After stirring at 60°C for 5 h the reaction mixture was neutralized with saturated aqueous sodium hydrogen carbonate and extracted with 3 x 25 ml of methylene chloride. The combined extracts were washed with water, dried and evaporated. The residue was purified on a Sephadex LH-20 column (87 x 2.5 cm) using chloroform as mobile phase. The fraction 455-510 ml was collected and evaporated giving 7 mg of (22S)-16α,17α-butylidenedioxy-6α-fluoro-11β-21-dihydroxypregn-4-ene-3,20-dione. Molecular weight 450 (calc. 450.6). Purity: 96.6%.

A solution of palmitoyl chloride (195 mg) in 5 ml of dioxane was added dropwise to a solution of (22S)-16α,17α-butylidenedioxy-6α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (32 mg) in 10 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 205-245 ml was collected and evaporated yielding 37 mg of (22S)-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione as an oil. Molecular weight 688 (calc. 688.97). Purity: 96.4% (HPLC-analysis).

Example 17. <u>(22RS)-16α,17α-Butylidenedioxy-6α-fluoro-11β-hydroxy-21-lauroyloxypregn-4-ene-3,20-dione</u>.
A solution of lauroyl chloride (0.4 ml) in 3 ml of dioxane was added dropwise to a solution of (22RS)-(16α,17α)-butylidenedioxy-6α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (50 mg) in 6 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purifi d

on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform: thanol, 20:20:1, as mobile phas . The fraction 215-250 ml was collect d and evaporated yielding 15 mg of (22RS)-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxy-21-lauroyloxypregn-4-ene-3,20-dione. Melting point 125-143°C. $[\alpha]_D^{25}$ = +92.8° (c=0.208; CH_2Cl_2). Molecular weight 632 (calc. 632.9). Purity: 96.2% (HPLC-analysis). The distribution between the 22R- and 22S-epimers was 58/42 (HPLC-analysis).

Example 18. (22R)-16α,17α-Butylidenedioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxypregna-1,4-diene-3,20-dione. 6α-Fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione (400 mg) was added in portions to a solution of butanal (0.18 ml) and 70% perchloric acid (0.2 ml) in 50 ml of dioxane. The reaction mixture was stirred at room temperature for 16 h. Methylene chloride (200 ml) was added and the solution washed with 10% aqueous potassium carbonate and water and dried. The residue after evaporation was purified on a Sephadex LH-20 column (75 x 6.3 cm) using chloroform as mobile phase. The fraction 2880-3300 ml was collected and evaporated yielding 1209 mg of (22RS)-16α,17α-butylidenedioxy-6α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione. Molecular weight 448 (calc. 448.5). The purity was 95.7% and the distribution between the 22R- and 22S-epimers 55/45 (HPLC-analysis).

(22RS)-16α,17α-Butylidenedioxy-6α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione (36 mg) was chromatographed on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fractions 1720-1800 ml (A) and 1960-2025 ml (B) were collected and evaporated. The two products were precipitated from methylene chloride - petroleum ether. Th product from fraction A (12 mg) was identified with ^{1}H-NMR and mass spectrometry to be (22S)-16α,17α-

butylidenedioxy-6α-fluoro-11β,21-dihydroxypr gna-1,4-dien -3,20-dione and th product from the B fraction (10 mg) as the 22R-epimer.

The epimers had the following properties. Epimer 22S: Melting point 172-180°C; [ ]$_D^{25}$ = +62.3° (c=0.132; CH_2Cl_2); molecular weight 448 (calc. 448.5). Epimer 22R: Melting point 95-106°C; $[\alpha]_D^{25}$ = +105.9° (c=0.152; CH_2Cl_2); molecular weight 448 (calc. 448.5). The purity of the epimers was determined by HPLC-analysis to be 98.9% for the 22S-epimer and 97.7% for the 22R-epimer.

A solution of palmitoyl chloride (172 mg) in 5 ml of dioxane was added dropwise to a solution of (22R)-16α,17α-butylidenedioxy-6α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione (56 mg) in 10 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 225-285 ml was collected and evaporated yielding 31 mg of (22R)-16α,17α-butylidenedioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxypregna-1,4-diene-3,20-dione. Melting point 95-100°C. $[\alpha]_D^{25}$ = +68.0° (c=0.200; CH_2Cl_2). Molecular weight 686 (calc. 686.95). Purity: 97.7% (HPLC-analysis).

Example 19. <u>(22S)-16α,17α-Butylidenedioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxypregna-1,4-diene-3,20-dione</u>. A solution of palmitoyl chloride (110 mg) in 5 ml of dioxane was added dropwise to a solution of (22S)-16α,17α-butylidenedioxy-6α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione (46 mg) in 10 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (89 x 2.5 cm) using

heptane:chloroform: thanol, 20:20:1, as mobile phase. Th fraction 185-225 ml was collected and evaported yielding 37 mg of (22S)-16α,17α-butyliden dioxy-6α-fluoro-11β-hydroxy-21-palmitoyloxypregna-1,4-diene-3,20-dione. Melting point 65-68°C. $[\alpha]_D$ = +53.0° (c=0.200; CH_2Cl_2). Molecular weight 686 (calc. 686.95). Purity: 95.9% (HPLC-analysis).

Example 20. 6α-Fluoro-11β,21-dihydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione.
A suspension of 2.1 g of tris(triphenylphosphine)rhodium chloride in 500 ml of toluene was hydrogenated at room temperature and atmospheric pressure for 45 min, when the catalyst was in solution. A solution of 2.0 g of 6α-fluoro-11β,21-dihydroxy-16α,17α-[(1-methylethylidene)bis-(oxy)]pregna-1,4-diene-3,20-dione in 1000 ml of absolute ethanol was added and the hydrogenation was continued for another 65 h. The reaction mixture was evaporated and the residue purified on a Sephadex LH-20 column (71 x 6.3 cm) using chloroform as mobile phase. The fraction 2010-2445 ml was collected and evaporated yielding 1.51 g of 6α-fluoro-11β,21-dihydroxy-16α,17α-[(1-methylethylidene)bis-(oxy)]pregn-4-ene-3,20-dione. Melting point 209-219°C. $[\alpha]_D^{25}$ = +133.5° (c=0.230; CH_2Cl_2). Molecular weight 436 (calc. 436.5). Purity: 99.6% (HPLC-analysis).

Example 21. 6α-Fluoro-11β-hydroxy-16α,17α-[(1-methyl-ethylidene)bis(oxy)]-21-palmitoyloxypregn-4-ene-3,20-dione.
A solution of palmitoyl chloride (0.21 ml) in 3 ml of dioxane was added dropwise to a solution of 6α-fluoro-11β,21-dihydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-pregn-4-ene-3,20-dione in 6 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (76 x 6.3 cm) using heptane:chloroform: thanol, 20:20:1, as mobile phase. Th

fraction 1035-1230 ml was collected and evaporated yielding 63 mg of 6α-fluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-21-palmitoyloxypregn-4-ene-3,20-dion . Melting point 99-101°C. $[\alpha]_D^{25}$ = +89.8° (c=0.206; CH_2Cl_2). Molecular weight 674 (calc. 674.94). Purity: 97.9% (HPLC-analysis).

Example 22. 9α-Fluoro-11β,21-dihydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]pregn-4-ene-3,20-dione.

A solution of 675 mg of tris(triphenylphosphine)rhodium chloride in 250 ml of toluene was hydrogenated at room temperature and atmospheric pressure for 45 min. A solution of 1 g of triamcinolone 16α,17α-acetonide in 100 ml of absolute ethanol was added and the hydrogenation was continued for another 40 h. The reaction mixture was evaporated and the main part of the catalyst removed by flash chromatography with aceton:petroleum ether (b.p. 40-60°C), 40:60, as mobile phase. The crude product was further purified on a Sephadex LH-20 column (72.5 x 6.3 cm) using chloroform as mobile phase. The fraction 2746-3195 ml was collected and evaported yielding 404 mg of 9α-fluoro-11β,21-dihydroxy-16α,17α-[(1-methylethylidene)-bis(oxy)]pregn-4-ene-3,20-dione. Melting point 238-41°C. $[\alpha]_D^{25}$ = +145.2° (c=0.288;CH_2Cl_2). Molecular weight 436 (calc. 436.5). Purity: 99% (HPLC-analysis).

Example 23. 9α-Fluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-21-palmitoyloxypregn-4-ene-3,20-dione.

A solution of palmitoyl chloride (0.69 ml) in 10 ml of dioxane was added dropwise to a solution of 9α-fluoro-11β,21-dihydroxy-16α,17α-[(1-methylethylidene)-bis(oxy)]pregn-4-ene-3,20-dione in 20 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The

fraction 240-305 ml was collect d and evaported yielding 102 mg of 6α-flu r -11β-hydroxy-16α,17α-[(1-m thylethylidene)bis(oxy)]-21-palmitoyloxypr gn-4-ene-3,20-dione as an oil. Molecular weight 674 (calc. 674.94). Purity: 98% (HPLC-analysis).

Example 24. (22RS)-16α,17α-Butylidenedioxy-9α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione.

To a solution of freshly distilled butanal (100 mg) and 0.2 ml of perchloric acid (70%) in 50 ml of purified and dried dioxane 9α-fluoro-11β,16α,17α,21-tetrahydroxypregn-4-ene-3,20-dione (340 mg) was added in small portions with stirring during 20 min. The reaction mixture was stirred at room temperature for another 5 h. Methylene chloride (200 ml) was added and the solution was washed with aqueous potassium carbonate and water and dried over anhydrous magnesium sulfate. The crude product obtained after evaporation was purified on a Sephadex LH-20 column (72.5 x 6.3 cm) using chloroform as mobile phase. The fraction 2760 - 3195 ml was collected and evaporated yielding 215 mg of (22RS)-16α,17α-butylidenedioxy-9α-fluoro-11β-21-dihydroxypregn-4-ene-3,20-dione. Molecular weight 450 (calc. 450.6). Purity: 97.4% (HPLC-analysis).

A solution of palmitoyl chloride (0.13 ml) in 2.5 ml of dioxane was added dropwise to a solution of (22RS)-16α,17α-butylidenedioxy-9α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (40 mg) in 5 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (87 x 2.5 cm) using chloroform as mobile phase. The fraction 220-300 ml was collected and evaporated yielding 42 mg of (22RS)-16α,17α-butylidene-dioxy-9α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dion as an oil. Molecular w ight 688 (calc. 688.97). Th distribution betw en the 22R- and 22S-epimers was

61/39 (HPLC-analysis).

Exampl 25. (22R)-16α,17α-Butylidenedioxy-9α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione. (22RS)-16α,17α-Butylidenedioxy-9α-fluoro-11β-21-dihydroxypregn-4-ene-3,20-dione (200 mg) was resolved by chromatography on a Sephadex LH-20 column (76 x 6.3 cm) using a heptane-chloroform-ethanol (20:20:1) mixture as mobile phase. The fractions 7560-8835 ml (A) and 8836-9360 ml (B) were collected and evaporated. The product from fraction A (128 mg) was identified with ^{1}H-NMR and mass spectrometry to be (22S)-16α,17α-butylidenedioxy-9α-fluoro-11β-21-dihydroxypregn-4-ene-3,20-dione and the product from the B fraction (50 mg) as the 22R-epimer.

The epimers had the following properties. Epimer 22S: Melting point 180-190°C; $[\alpha]_D^{25}$ = +105.6° (c=0.214; CH_2Cl_2 molecular weight 450 (calc. 450.6). Epimer 22R: Melting point 147-151°C; $[\alpha]_D^{25}$ = +133.7° (c=0.196; CH_2Cl_2); molecular weight 450 (calc. 450.6). The purity of the epimers was determined by HPLC-analysis to be 95.6% for the 22S-epimer and 98.2% for the 22R-epimer.

A solution of palmitoyl chloride (0.34 ml) in 5 ml of dioxane was added dropwise to a solution of (22R)-16α,17α-butylidenedioxy-9α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (50 mg) in 10 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 180-205 ml was collected and evaporated yielding 36 mg of (22R)-16α,17α-butylidenedioxy-9α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione as an oil. Purity: 96.3% (HPLC-analysis). Molecular weight 688 (calc. 688.97).

Example 26. (22S)-16α,17α-Butylidenedioxy-9α-fluoro-11β-hydroxy-21-palmitoyloxypr gn-4-ene-3,20-dion .
A solution of palmitoyl chloride (0.14 ml) in 15 ml of dioxane was added dropwise t a soluti n of (22S)-16α,17α-butylidenedioxy-9α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione (41 mg) in 3 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (89 x 2.5 cm) using heptane:chloroform:ethanol, 20:20:1, as mobile phase. The fraction 215-260 ml was collected and evaporated yielding 26 mg of (22S)-16α,17α-butylidenedioxy-9α-fluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione as an oil. Purity: 91.4% (HPLC-analysis). Molecular weight 688 (calc. 688.97).

Example 27. (22R)-16α,17α-Butylidenedioxy-9α-fluoro-11β-hydroxy-21-palmitoyloxypregna-1,4-diene-3,20-dione.
A solution of palmitoyl chloride (75 mg) in 2.5 ml of dioxane was added dropwise to a solution of (22R)-16α,17α-butylidenedioxy-9α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione (25 mg) in 5 ml of pyridine. The reaction mixture was stirred at room temperature overnight and worked up as in Example 1. The crude product was purified on a Sephadex LH-20 column (85 x 2.5 cm) using chloroform as mobile phase. The fraction 235-285 ml was collected and evaporated yielding 27 mg of (22R)-16α, 17α-butylidenedioxy-9α-fluoro-11β-hydroxy-21-palmitoyl-oxypregna-1,4-diene-3,20-dione. Melting point 116-121°C; $[\alpha]_D^{25}$ = +67.4° (c=0.172;CH_2Cl_2). Molecular weight 686 (calc. 687.0). Purity: 96.5% (HPLC-analysis).

Example 28. Pharmaceutical Preparations
The following non-limitative examples illustrate formulations intended for different topical forms of administration. The amount of active steroid in the

percutaneous formulations are ordinarily 0.001-0.2% (w/w), pref rably 0.01-0.1% (w/w).

Formulation 1, Ointment

Steroid, micronized		0.025 g
Liquid paraffin		10.0 g
White soft paraffin	ad	100.0 g

Formulation 2, Ointment

Steroid		0.025 g
Propylene glycol		5.0 g
Sorbitan sesquioleate		5.0 g
Liquid paraffin		10.0 g
White soft paraffin	ad	100.0 g

Formulation 3, Oil in water cream

Steroid		0.025 g
Cetanol		5.0 g
Glyceryl monostearate		5.0 g
Liquid paraffin		10.0 g
Cetomacrogol 1000		2.0 g
Citric acid		0.1 g
Sodium citrate		0.2 g
Propylene glycol		35.0 g
Water	ad	100.0 g

Formulation 4, Oil in water cream

Steroid, micronized		0.025 g
White soft paraffin		15.0 g
Liquid paraffin		5.0 g
Cetanol		5.0 g
Sorbimacrogol stearate		2.0 g
Sorbitan monostearate		0.5 g
Sorbic acid		0.2 g
Citric acid		0.1 g

Sodium citrate		0.2	g
Water	ad	100	g

Formulation 5, Water in oil cream

Steroid		0.025	g
White soft paraffin		35.0	g
Liquid paraffin		5.0	g
Sorbitan sesquioleate		5.0	g
Sorbic acid		0.2	g
Citric acid		0.1	g
Sodium citrate		0.2	g
Water	ad	100.0	g

Formulation 6, Lotion

Steroid		0.25	mg
Isopropanol		0.5	ml
Carboxyvinylpolymer		3	mg
NaOH		q.s.	
Water	ad	1.0	g

Formulation 7, Suspension for injection

Steroid, micronized		0.05-10	mg
Sodium carboxymethylcellulose		7	mg
NaCl		7	mg
Polyoxyethylene (20) sorbitan monooleate		0.5	mg
Phenyl carbinol		8	mg
Water, sterile	ad	1.0	ml

Formulation 8, Aerosol for oral and nasal inhalation

Steroid, micronized	0.1	% w/w
Sorbitan trioleate	0.7	% w/w
Trichlorofluoromethane	24.8	% w/w
Dichlorotetrafluoromethane	24.8	% w/w
Dichlorodifluoromethane	49.6	% w/w

Formulation 9, Solution for atomization

Ster id		7.0 mg
Pr pylene glycol		5.0 g
Water	ad	10.0 g

Formulation 10, Powder for inhalation

A gelatin capsule is filled with a mixture of

Steroid, micronized	0.1 mg
Lactose	20 mg

The powder is inhaled by means of an inhalation device.

Formulation 11, Powder for inhalation

The spheronized powder is filled into a multidose powder inhaler. Each dose contains

Steroid, micronized	0.1 mg

Formulation 12, Powder for inhalation

The spheronized powder is filled into a multidose powder inhaler. Each dose contains

Steroid, micronized	0.1 mg
Lactose, micronized	1 mg

Formulation 13, capsule for treating the small bowel

Steroid	1.0 mg
Sugar spheres	321 mg
Aquacoat ECD 30	6.6 mg
Acetyltributyl citrate	0.5 mg
Polysorbate 80	0.1 mg
Eudragit L100-55	17.5 mg
Triethylcitrate	1.8 mg
Talc	8.8 mg
Antifoam MMS	0.01 mg

Formulation 14, capsule for treating the large bowel

Steroid	2.0 mg
Sugar sph res	305 mg

Aquacoat ECD 30		5.0 mg
Ac tyltributyl citrate		0.4 mg
Polys rbate 80		0.14 mg
Eudragit NE30 D		12.6 mg
Eudragit S100		12.6 mg
Talc		12.6 mg

Formulation 15, rectal enema

Steroid		0.02 mg
Sodium carboxymethylcellulose		25 mg
Disodium edetate		0.5 mg
Methyl parahydroxybenzoate		0.8 mg
Propyl pharahydroxybenzoate		0.2 mg
Sodium chloride		7.0 mg
Citric acid anhydrous		1.8 mg
Polysorbate 80		0.01 mg
Water, purified	ad	1.0 ml

Formulation 16, formulation containing liposomebound steroid

A. Preparation of a formulation for instillation

Synthetic dipalmitoylphosphatidylcholine (45 mg), dimyristoylphosphatidylcholine (7 mg), dipalmitoyl-phosphatidylglycerol (1 mg) and (22R)-16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-21-palmitoyloxypregn-4-ene-3,20-dione (5 mg) are mixed in a glass tube. All components are dissolved in chloroform. Most of the solvent is evaporated by the use of N_2 and then under reduced pressure, which forms a thin film of the lipid components on the surface of the glass tube. An aqueous solution (0.9% NaCl) is added to the lipids. Formation of the liposomes is performed at a temperature above the phase transition temperature of the lipids. The liposomes are formed by shaking or sonication of the solution with the probe of a sonicator. The r sulting suspension contains liposomes ranging from very small

vesicles to 2 µm in siz .

B. Preparation of a formulation for inhalation

The pr parati n of the liposomes is performed according to Example A, where the aqueous solution contains 10% lactose. The ratio between lactose and lipid is 7:3. The liposome suspension is frozen on dry ice and lyophilized. The dry product is micronized resulting in particles with a mass mean aerodynamic diameter (MMAD) of about 2 µm.

Pharmacology

The selectivity for local antiinflammatory activity can be exemplified by the following airway model.

A considerable fraction of inhaled GCS is deposited in the pharynx and is subsequently swallowed ending up in the gut. This fraction contributes to the unwanted side effects of the steroid since it is acting outside the area intended for treatment (the lung). Therefore, it is favourable to use a GCS with high local anti-inflammatory activity in the lung but low GCS induced effects after oral administration. Studies were therefore done in order to determine the GCS induced effects after local application in the lung as well as after per oral administration and the differentiation between glucocorticosteroid actions in the treated lung region and outside this area were tested in the following way.

Test models

A) Test model for desired local antiinflammatory activity on airway mucosa (left lung lobe).

Sprague Dawley rats (250 g) were slightly anaesthetized with Ephrane and the glucocorticosteroid test preparation (in liposomes suspended in saline) in a volume of 0.5 ml/kg was instilled into just the l ft lung lob . Two

hours later a suspension of Sephad x (5 mg/kg in a volume of 1 ml/kg) was instilled in th trachea well abov the bifurcation so that the suspension reached both th left and right lung lobes. Twenty hours later the rats were killed and the left lung lobes dissected out and weighed. Control groups got vehicle instead of glucocorticosteroid preparation and saline instead of Sephadex suspension to determine the weight of non-drug treated Sephadex edema and the normal lung weight.

B) Test model for unwanted systemic effect by orally absorbed glucocorticosteroid

Sprague Dawley rats (250 g) were slightly anaesthetized with Ephrane and the GCS test preparation in a volume of 1.0 ml/kg was given orally. Two hours later a suspension of Sephadex (5 mg/kg in a volume of 1 ml/kg) was instilled in the trachea well above the bifurcation so that the suspension reached both the left and the right lung lobes. Twenty hours later, the rats were killed and the lung lobes were weighed. Control groups got vehicle instead of glucocorticosteroid preparation and saline instead of Sephadex suspension to determine the weight of non-drug treated Sephadex edema and the normal weight.

The results of the comparative study are given in Table 1. The pharmacological profile of the compounds of the invention was compared to those of budesonide-21-palmitate and flumethasone-21-palmitate in liposomes. All steroids of the invention show higher local anti-inflammatory potency in the lung after local application than budesonide-21-palmitate in liposomes. Furthermore, the results also demonstrate a higher lung selectivity of the tested compounds of the invention compared to the selected prior art compounds, since the dose required to inhibit lung edema (ED_{50}) by oral administration of the above mentioned compounds are 158 (example 3), 247 (example 7) and 559 (exampl 1) times higher and of bud sonide-21-

palmitate 66 times higher and of flum thasone-21-palmitat 8 tim s higher than the dose ne ded to inhibit lung edema by local application to the lung of th drugs.

Thus it can be concluded that the compounds of the invention are well suited for local treatment of inflammatory disorders in the skin and various cavities of the body (e.g. lung, nose, bowel and joint).

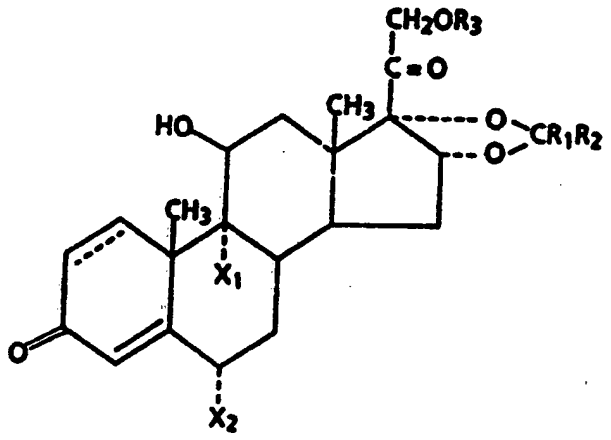
Table 1. Effects of tested glucocorticosteroids in liposomes in the Sephadex induced lung edema model in the rat. The results are given in relation to the corresponding control group given Sephadex.

Compound according to example	ED_{50} (left lung administration; nmol/kg) Left lung lobe x)	ED_{50} (p.o.adm.; nmol/kg) lung x)	Ratio oral/local administration
Budesonide-21-palmitate (RS)	23	1520	66
Flumethasone-21-palmitate	2.2	18	8
7	2.3	568	247
6	1.8	-	
3	3.5	554	158
1	1.5	839	559

x) ED_{50} = required glucocorticosteroid dose to reduce the edema by 50%.

Claims

1. A compound of the general formula



I

or a stereoisomeric component thereof, in which formula the 1,2-position is saturated or is a double bond,

R_1 is hydrogen or a straight or branched hydrocarbon chain having 1-4 carbon atoms,

R_2 is a hydrogen or a straight or branched hydrocarbon chain having 1-10 carbon atoms,

R_3 is acyl having a straight or branched, saturated or unsaturated hydrocarbon chain having 1-20 carbon atoms,

X_1 is hydrogen or halogen

X_2 is hydrogen or halogen and

provided that

1) R_1 and R_2 are not simultaneously hydrogen,
2) X_1 and X_2 are not simultaneously hydrogen,
3) when the 1,2-position is a double bond, R_1 and R_2 are not simultaneously methyl groups,
4) when the 1,2-position is a double bond, R_1 is a hydrogen atom and R_2 is a straight or branched hydrocarbon chain having 1-10 carbon atoms R_3 is acyl having 11-20 carbon atoms.

2. A compound according t claim 1, wher in the general formula I the 1,2-position is saturated

R_1 is hydrogen or a straight or branched hydrocarbon chain having 1-4 carbon atoms,

R_2 is a hydrogen or a straight or branched hydrocarbon chain having 1-10 carbon atoms,

R_3 is acyl having a straight or branched, saturated or unsaturated hydrocarbon chain having 1-20 carbon atoms,

X_1 is hydrogen or halogen,

X_2 is hydrogen or halogen, and

provided that

1) R_1 and R_2 are not simultaneously hydrogen and

2) X_1 and X_2 are not simultaneously hydrogen.

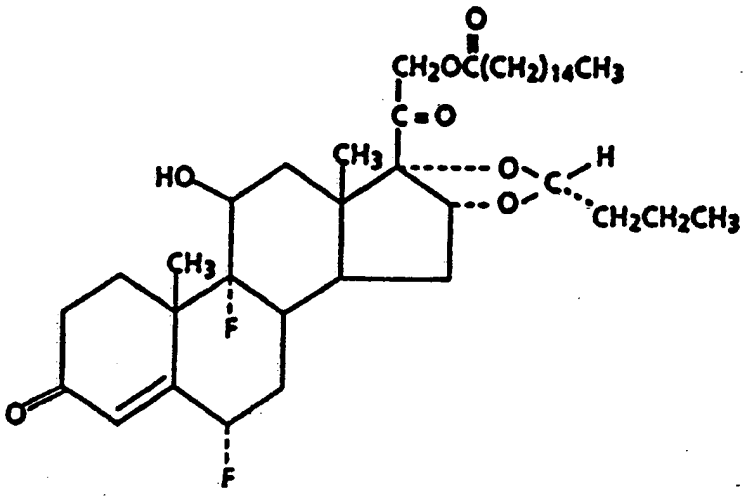
3. A compound according to any of claims 1-2, wherein R_3 is acyl having 11-20 carbon atoms.

4. A compound according to any of claims 1-2 wherein R_3 is acyl having 1-10 carbon atoms.

5. A compound according to claim 3 wherein the 1,2-position is saturated, R_1 is a hydrogen atom, R_2 is a propyl group, X_1 is fluorine and X_2 is fluorine.

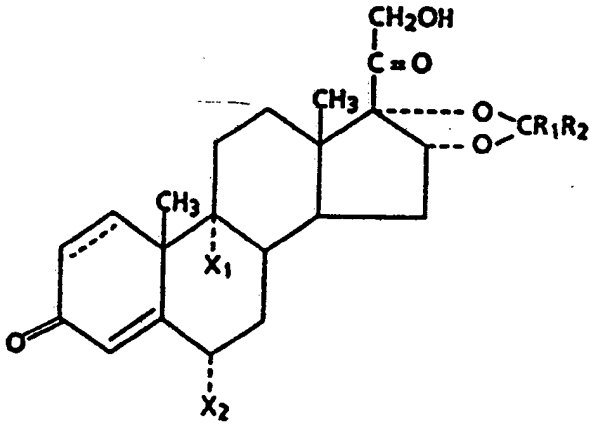
6. A compound according to claim 1 wherein the 1,2-position is a double bond, R_1 is a hydrogen atom, R_2 is a propyl group, R_3 is a palmitoyl group, X_1 is fluorine and X_2 is fluorine.

7. A compound according to claim 1 having th f rmula



8. A process for the preparation of a compound of the general formula I as defined in claim 1, characterized by

a) reaction of a compound of the formula

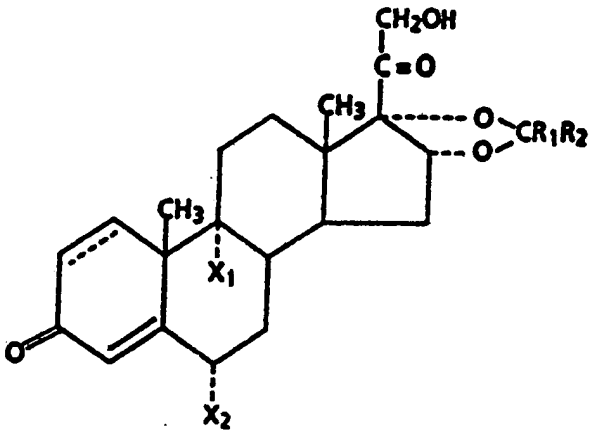


wherein R_1, R_2, X_1 and X_2 are as defined in claim 1, with a compound of the formula

$$R_4COOH$$

wherein R_4 is a straight or branch d, saturated or unsaturated alkyl with 1-19 carbon atoms, or

b) reaction of a compound of the formula

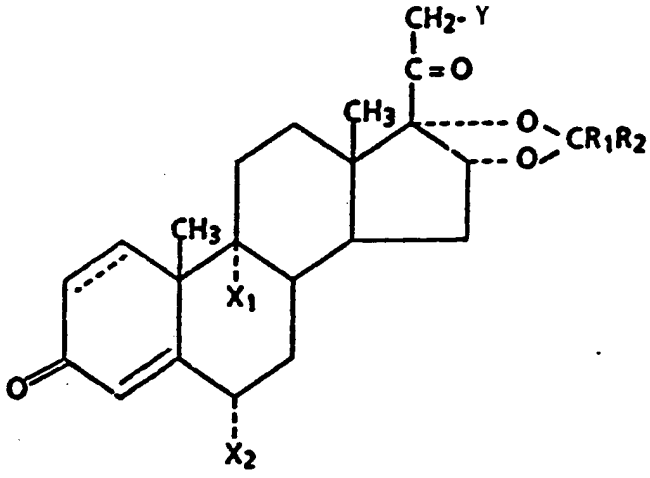


wherein R_1, R_2, X_1 and X_2 are as defined in claim 1, with a compound of the formula

$$R_4COX$$

wherein R_4 is as defined above and X is a halogen atom or the moiety $-OOCR_4$, or

c) reaction of a compound of the formula



wherein R_1, R_2, X_1 and X_2 are as d fined in claim 1 and Y

is halog n, mesylate or p-toluenesulfonate, with a compound of the formula

$$R_4COO^{\ominus}{}_A{}^{\oplus}$$

wherein R_4 is as defined above and $A^{\oplus}$ is a cation, whereafter, if the thus obtained compound is an epimeric mixture and a pure epimer is desired, resolving the epimeric mixture into its stereoisomeric components.

9. A process according to claim 8 characterized in that a compound according to any of claims 2-7 is prepared.

10. A pharmaceutical preparation comprising as active ingredient a compound according to any of claims 1-7.

11. A pharmaceutical preparation according to claim 10 containing liposomes including a pharmacologically active compound according to claim 3.

12. A pharmaceutical preparation according to claims 10-11 in dosage unit form.

13. A pharmaceutical preparation according to claims 10-12 comprising the active ingredient in association with a pharmaceutically acceptable carrier.

14. A compound according to any of claims 1-7 for use as a therapeutically active substance.

15. Use of a compound according to any of claims 1-7 for the preparation of medicaments with anit-inflammatory and anti-allergic activity.

16. A method for the treatment of inflammatory and allergic conditions in mammals, including man, characteriz d by the administration to a host in n ed f

such treatment of an effective amount of a compound according to any of claims 1-7.

17. Compounds and processes for their preparation, pharmaceutical compositions containing them, and their use in the treatment of inflammatory and allergic conditions as claimed in claim 1-16 inclusive and substantially as described.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 92/00056

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 J 71/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 J

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in Fields Searched[8]

SE,DK,FI,NO classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	ACTA PHARM.SUEC., Vol. 21, 1984 Arne Thalén et al: "Synthesis and pharmacological properties of some 16x,17x-acetals of 16x-hydroxyhydrocortisone, 16x-hydroxyprednisolone and fluorinated 16x-hydroxyprednisolones", page 109-124, see particularly page 113 --	1,2,4,8-10,12-15,17
X	Patent Abstracts of Japan, Vol 9, No 200, C298, abstract of JP 60- 67496, publ 1985-04-17 (OOTA SEIYAKU K.K.) --	1,2,4,8-10,12-15,17
X	EP, A2, 0170642 (AKTIEBOLAGET DRACO) 5 February 1986, see the whole document --	1-15, 17

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
8th May 1992	1992 -05- 12
International Searching Authority	**Signature of Authorized Officer**
SWEDISH PATENT OFFICE	Eva Johansson Eva Johansson

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	US, A, 4695625 (MACDONALD) 22 September 1987, see the whole document --	1-3,5,8-15,17
A	US, A, 3929768 (BRATTSAND ET AL) 30 December 1975, see the whole document --	1-15, 17
A	US, A, 3197469 (JOSEF FRIED) 27 July 1965, see the whole document --	1-15, 17
A	EP, A2, 0164636 (SICOR SOCIETA ITALIANA CORTICOSTEROIDI S.P.A.) 18 December 1985, see the whole document --	1-15, 17

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 16., because ~~they~~ it relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(IV). Method for treatment of the human or animal body by surgery or therapy as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the the claims. It is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additonal fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional seach fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 92/00056

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on 28/03/92 The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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